selectively hybridizing under stringent hybridization conditions to said adapter sequence, and the other primer selectively hybridizing, under stringent hybridization conditions, to said transposable element.

17. (Twice Amended) The method of claim 15, further comprising a second amplification to preferentially amplify adapter-modified DNA fragments, wherein said second amplification employs at least two oligonucleotide primers, with one of said primers selectively hybridizing under stringent hybridization conditions to said adapter sequence and the other primer selectively hybridizing under stringent hybridization conditions to said transgene.

REMARKS

Claims 1-21 are under examination and pending in the case. Claims 9 and 17 have been amended. Support for the amendments is found in the specification as filed. No new matter has been added. In the previous amendment, Applicants' representative failed to carry forward some of the amendments to claims 9 and 17 in the marked-up version of the claims. In a discussion with Examiner Tung on January 14th, Applicants' representative was instructed to re-amend claims 9 and 17 using the claims in the previous amendment's marked-up version as a starting point.

35 U.S.C. §112, 2nd Paragraph

Claims 9 and 17 were rejected under section 112, second paragraph, because it was unclear where the phrase "said preliminary amplification" was referenced. Claims 9 and 17 have been amended to eliminate improper antecedent basis that was the basis of the rejection. Accordingly, withdrawal of the rejection is kindly requested.

35 U.S.C. §103

Claims 1, 4-8, 10-13, 15-16, and 18-21 were rejected under 35 U.S.C. §103(a) as being unpatentable over Straus *et al.* (PNAS USA 87:1889-1893 (1990) in view of Lindemann *et al.* (U.S. Pat. No. 5,958,738), Walbot *et al.* (Mol. Gen. Genet. 211:27-34 (1988), and Briggs *et al.* (U.S. Pat. No. 5,962,764) for reasons made of record in the previous Office action.

Applicants respectfully submit that the Office Action fails to make a proper *prima facie* case of obviousness. According to the M.P.E.P. §2143:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed Cir. 1991) (emphasis added).

Applicants' contend that the references cited by the Examiner fail to provide the requisite suggestion or motivation to make the claimed invention as is required to sustain a rejection under 35 U.S.C. §103.

A. Straus *et al.* Is Inoperable as Modified for the Claimed Invention

The Federal Circuit has stated clearly on several occasions that if a proposal for modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. *In re Fritsch* 23 USPQ2d 1780, 1783 (Fed. Cir. 1992); *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). From this, it follows that no motivation to make the claimed invention can exist if the genomic subtraction scheme of Straus *et. al.* is inoperable as applied to the claimed invention. In other words, if the genomic subtraction scheme of Straus *et. al.* cannot function if

modified for use with the claimed invention then no incentive to modify Straus *et. al.* to achieve the claimed invention can be present. And if there is no motivation or suggestion then the rejection for obviousness cannot be sustained.

Straus *et. al.* teach a method of genomic subtraction for cloning DNA corresponding to deletion mutations. At the first full paragraph on page 1893 it states, "The application of genomic subtraction is subject to several constraints. Strains with homozygous or hemizygous deletions of the locus to be cloned must be available and viable." But in the claimed invention no such homozygous or hemizygous deletions are present. Rather, and in sharp contrast, the claimed invention relates to methods involving genomic insertions. Claim 1, step (a) recites segregating organisms "wherein the genomic DNA of each organism comprises at least one copy of said transposable element" (emphasis added). Thus, in this embodiment of the claimed invention neither of the two segregated populations are missing DNA relative to the other population, rather the difference is in the location(s) of the transposable element(s). In claim 15, the method is directed to identifying the location of a transgene insertion. Again, in this aspect of the claimed invention the organisms differ not in the presence or absence of the transgene but in its location. Nowhere in the discussion of their technique does Straus *et al.* teach or suggest that their method is applicable to insertions. On the contrary, they teach its inapplicability to mutants not having a homozygous or hemizygous deletion.

The method of Straus *et. al.* is entirely dependent upon the two DNA samples differing as to the deleted DNA that is eventually to be identified. By subtracting out DNA common to wild-type and mutant samples one can isolate DNA that is absent in the deletion mutant. However, in the claimed invention the DNA to be isolated and identified is present in all organisms under study; it merely differs as to its location in the genome. Since there is no DNA missing relative to one of the samples, Straus *et. al.* is not merely an inefficient method to adapt to the claimed invention, rather it is an entirely ineffective and inoperable method. Since Straus *et. al.* cannot be modified for

invention, the rejection under §103 must be withdrawn.

C. Lindemann *et al.* Is Inoperable as Modified for the Claimed Invention

In the discussion of Straus *et al.*, mention has already been made of the Federal Circuit's position that modifying the prior art in such a way as to render the art inoperable for its intended purpose cannot constitute motivation to make the modification. The same argument applies to the reference of Lindemann *et al.* which, like Straus *et al.*, is drawn to a method of subtractive hybridization. In the patent of Lindemann *et al.* the objective is identifying a nucleic acid that is absent in one population relative to another. In contrast, the presently claimed invention is drawn to insertions that differ not with respect to absence or presence but as to their position in the genome. Lindemann *et al.* make the differential nature of their invention very clear at column 5, lines 60-64, where it states,

> The invention provides improved methods for the identification and isolation of polynucleotides comprising nucleic acid sequences present in a first (sample) cell, cell type, or cell population that are not present in one or more other (control) cell(s), cell type(s) or cell population(s). (emphasis added).

Nowhere does *Lindemann et al.* teach or suggest that their method is applicable to the populations employed in the claimed invention where transposable elements are present in both sample and control populations. Indeed, if Lindemann *et al.* employed control and sample populations such as those employed in the claimed invention then Lindemann *et al.* would not work for its intended function. Neither would the teachings of Lindemann *et al.* prove itself operable in identifying the location of a transgene in which all organisms used in the method contain the transgene but may differ as to the locus of its insertion. No motivation can be found for a modification to an inoperable method and, consequently, Lindemann *et al.* cannot be employed to argue for the required motivation under section 103.

D. Motivation Cannot be Found in Applicants' Specification

The Examiner has argued that Lindemann *et al.* suggest that the primer is nested as recited in the pending claim set and that the oligonucleotide of Lindemann *et al.* has the same function as the adapter recited in the pending claim set. Page 3, lines 1-5. Walbot *et al.* is cited as teaching a primer specific to a transposable element to be used for polymerase chain reaction. Page 3, lines 6-8. Briggs *et al*, Grunder *et al.* and Halverson *et al.* are also cited as reciting one or more elements present in the pending claims. Using this approach, the Examiner attempts to argue obviousness of the claimed invention by reference to a collection of its component parts. But it is not sufficient that various elements of the claimed invention can be found among the disclosures of multiple separate references, leaving the practitioner pick and choose disparate elements from among several cited references. Rather there must be a motivation, not in Applicants' disclosure, but in the prior art that would lead a practitioner skilled in the art to select and combine the elements found in the separate documents.

The Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not applicant's specification. See, *In re Dow Chem Co. V. American Cyanamid*, 5 USPQ2d at 1531-1532 (Fed. Cir. 1988). In the case of the subject claims, while some limitations of the claims may arguably be found amongst the cited references, none of the references either alone or in combination provide the motivation mandated by law and made abundantly clear at M.P.E.P. §2143. One the contrary, the inoperability of the methods of Straus *et al.* and Lindemann *et al.* as discussed in sections (A) and (C) above refute any contention that these references can provide the motivation that is necessary in establishing a *prima facie* case of obviousness.

E. Briggs *et al.* Doesn't Correct the Deficiencies of the Other References

Briggs *et al.* is a reverse genetics technique that associates a phenotype with insertional inactivation of a gene. In other words, it helps associate a function with a

known gene. Using the method of Briggs *et al.* a researcher who wishes to identify the function of a gene in a plant can isolate seed in which that gene has been inactivated. The mutant phenotype of the plant grown from that seed can shed light on the gene's function. In contrast, the present invention helps identify a gene for a known phenotype. Thus, the present invention is, in part, a forward genetics technique. Unlike the method of Briggs *et al.* the mutant phenotype in the present invention is not discovered afterwards, rather it must be known *a priori*. If the mutant phenotype of interest is not know beforehand then the segregation step of claim 1 step (a) cannot be achieved. As for claim 15, Briggs *et al.* may recite some elements employed in identifying the locus of transgene insertion but mere recitation of one or more components that might be useful in the claimed invention does not rise to the requisite suggestion or motivation to make the claimed invention. Applicants' specification cannot properly be used to provide the incentive that is entirely lacking in the prior art. Briggs *et al.*, neither alone nor in combination with the other references cited by the Examiner, corrects the deficiencies addressed previously in this response.

F. Neither Grunder *et al.* nor Halverson *et al.* Correct the Deficiencies in the Prima Facie Case

Grunder *et al.* is cited as teaching cosegregation analysis. Halverson *et al.* is cited as teaching bulked segregant analysis. But neither of the elements cited from these references can act to salvage the lack of incentive or motivation to make the claimed invention. The Examiner cannot simply identify references disclosing various elements of the claimed invention and then conclude that mere possession of them would provide motivation to make the claimed invention. It is impermissible to employ hindsight reconstruction using the Applicants' disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art. The Federal Circuit has held that such an approach contravenes the statutory mandate of §103 of judging obviousness at the point in time when the invention was made. See, *Grain Processing Corp v. American*

Maize-Prods, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988). As such, neither Grunder *et al.* nor Halverson *et al.* can properly be found to provide the motivation to make the claimed invention.

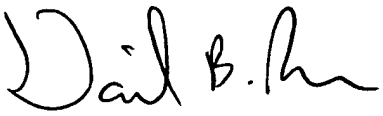
G. The Rejection Cannot be Sustained Without Motivation to Make the Claimed Invention

In summary, Applicants contend that Straus *et al.* is inoperable as modified to function for the present invention and thus cannot lawfully be cited as providing incentive to make the invention of claim 1 or 9 nor any of their dependent claims. Furthermore, Straus *et al.* expressly teaches away from adding adaptors prior to isolation and thus teach away from the invention of claim 1. Lindemann *et al.* also is inoperable as modified for the claimed invention and likewise cannot be found to provide the required incentive to make the invention of claim 1 or 9. The method of Briggs *et al.* helps to identify the phenotype associated with a gene of known sequence. This situation is reversed from that of claim 1 which requires that the phenotype be known beforehand so that the gene associated with the phenotype can be identified. Grunder *et al.* and Halverson *et al.* do nothing more than teach isolated elements recited in claims dependent from claim 1 which is insufficient to provide the requisite motive to make the claimed invention. In view of the deficiencies of the prior art in meeting the requirements needed to sustain a rejection for *prima facie* obviousness, Applicants kindly request withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

For the foregoing reasons, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112 and §103 and passage of the application to issuance. In the event that any issues of substance remain, **APPLICANTS HEREBY REQUEST AN EXAMINER INTERVIEW PRIOR TO PREPARATION OF ANY ADDITIONAL WRITTEN ACTION BY THE EXAMINER.** Please feel free to call the undersigned to arrange for an Examiner's interview or to discuss the status of the application.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

9. The method of claim 1, further comprising a second amplification to preferentially amplify adapter-modified DNA fragments, wherein said [preliminary amplification] second amplification employs at least two oligonucleotide primers, with one of said primers selectively hybridizing under stringent hybridization conditions to said adapter sequence, and the other primer selectively hybridizing, under stringent hybridization conditions, to said transposable element.

17. The method of claim 15, further comprising a second amplification to preferentially amplify adapter-modified DNA fragments, wherein said [preliminary amplification] second amplification employs at least two oligonucleotide primers, with one of said primers selectively hybridizing under stringent hybridization conditions to said adapter sequence and the other primer selectively hybridizing under stringent hybridization conditions to said transgene.